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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|--|-------------|----------------------|---------------------|------------------|
| 09/904,485 | 07/13/2001 | Avi Ashkenazi | 10466/44 | 8938 |
| 30313 | 7590 | 10/01/2004 | EXAMINER | |
| KNOBBE, MARTENS, OLSON & BEAR, LLP 2040 MAIN STREET IRVINE, CA 92614 | | | SAOUD, CHRISTINE J | |
| | | ART UNIT | | PAPER NUMBER |
| | | 1647 | | |

DATE MAILED: 10/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

| | | |
|--------------------|------------------|--|
| Application No. | Applicant(s) | |
| 09/904,485 | ASHKENAZI ET AL. | |
| Examiner | Art Unit | |
| Christine J. Saoud | 1647 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
 - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 12 July 2004.
2a) This action is FINAL. 2b) This action is non-final.
3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 39-46 and 49-51 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5) Claim(s) _____ is/are allowed.
6) Claim(s) 39-46 and 49-51 is/are rejected.
7) Claim(s) _____ is/are objected to.
8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
5) Notice of Informal Patent Application (PTO-152)
6) Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 12 July 2004 has been entered.

Response to Amendment

Claims 39-46 have been amended and claims 47-48 are canceled as requested in the amendment 12 July 2004. Claims 39-46, 49-51 are pending in the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

Applicant's arguments filed 12 July 2004 have been fully considered but they are not deemed to be persuasive.

Priority

Applicant asserts that U.S. Application No. 60/100,858, filed September 17, 1998 discloses stimulatory activity in MLR (mixed lymphocyte reaction) assay and that the data generated in the MLR assay (Example 74) establish patentable utility (see response at page 5). However, a review of the instant application and this assay do not lead to a conclusion of utility based on this assay, and therefore, priority to this provision application is not afforded for the reasons of record. The effective filing date of the instant application is still based on the disclosure PCT/US00/04414, filed 2/22/2000 for the reasons of record.

Response to Arguments

Applicant argues at page 7 of the response that a *prima facie* case of lack of utility has not been established. First, it should be made clear that the claimed invention has met the utility requirement based on its activity of inhibiting VEGF stimulated proliferation of adrenal cortical capillary endothelial cells. However, the invention lacks utility based on the assertion that the claimed invention could be used therapeutically to enhance the immune response in an individual. The instant specification discloses that the claimed protein (PRO217 – SEQ ID NO:4) tested positive in the MLR assay wherein

"positive increases over control are considered positive" (see pages 208-209 of the specification).

In the previous Office actions, several references were provided in order to support the position that the MLR assay is not predictive of general immune responses *in vivo*, but is art recognized for determining histocompatibility, among other things. Applicant states at page 7 of the response that "the Examiner has failed to point out several instances quoted within these references wherein the authors stated that MLR is an important method with a good predictive value". Applicant's arguments are not persuasive because the Examiner evaluated the references and the assay in question as they pertained to the asserted use of the claimed invention, which is for therapeutic enhancement of the immune response of an individual. If the claimed invention is to be used for therapeutic enhancement of the immune response of an individual, the question to ask is how are the results of the MLR assay related to the asserted utility of the claimed invention? The previous Office actions go into great depth regarding the nature of the MLR assay and how those skilled in the art use this assay and what kind of determinations can be made about compounds which are tested in this assay. The predictive nature of the MLR assay for transplantation and alloimmune response were pointed out in the previous Office actions and support the position that the MLR assay has not been shown to be predictive for general immune responses *in vivo* because it is a special case of antigen stimulation in which T lymphocytes respond to foreign histocompatibility antigen on unrelated lymphocytes or monocytes. As pointed out previously, this reaction is not predictive of general responses of the immune system

because, *in vivo*, activation of a lymphocyte is controlled not only by antigen binding but also by interactions with other cells. MLC (a.k.a. MLR) assay is a measure of alloreactivity of one individual to another individual, rather than a general measure of immune function. This reactivity is governed by the antigenic disparity between the two individuals which are being compared in the assay. Depending on the individuals being tested, the MLC may indicate stimulation if they are HLA-disparate or the MLC may indicate no stimulation if the individuals are HLA-identical. The ability of the claimed invention to stimulate proliferation in the MLC assay may not be a general stimulus to lymphocyte proliferation, but rather a reaction to one of the MHC antigens on the responder cell. The instant specification fails to provide sufficient detail of the assay which was performed and fails to provide any data whatsoever in order for one of ordinary skill in the art to evaluate the conclusion that lymphocyte proliferation was stimulated by the claimed invention. As pointed out previously, there are several controls which the art recognizes as being essential for meaningful results for this assay, including autologous controls, a control to determine maximum response, screening for possible HLA antibodies and growth support capabilities. Furthermore, there is known inherent variability of individual cellular responses from day to day, which would clearly dictate the need for internal controls. The specification indicates that CD4-IgG was used as a control, but it is not clear how this would control for background stimulation or provide for a measure of maximal stimulation. Lastly, the specification fails to provide any data or evidence of the results of the assay, therefore, one of ordinary skill in the art cannot evaluate the conclusion. The specification states that

"positive increases over control are considered positive", however, this does not indicate that statistical significance must occur for determination of a positive result in the assay. In conclusion, the results of the MLC (a.k.a. MLR) assay do not support a specific and substantial utility for the claimed invention because the assay is not predictive of immune response in general, and one of ordinary skill in the art would not expect a stimulatory effect in the MLC assay to correlate to a general stimulatory effect on the immune system, absent evidence to the contrary.

The Declaration under 37 CFR 1.132 filed 12 July 2004 is insufficient to overcome the holding of lack of utility based on results of the MLR assay. At paragraph #8 of the Declaration, Dr. Fong states "[t]he MLR assay of the present application is designed to measure the ability of a test substance to "drive" the dendritic cells to induce the proliferation of T-cells that are activated, or co-stimulated in the MLR, and thus identifies immune stimulants that can boost the immune system to respond to a particular antigen that may not have been immunologically active previously". This is not what the instant specification asserts at pages 208-209. There is no mention in the instant specification about boosting the immune system "to respond to a particular antigen that may not have been immunologically active previously". It would appear that Dr. Fong is reading the results of the Peterson et al. reference into the disclosure of the instant specification. However, the Peterson et al. reference was not available at the time the instant application was filed, therefore, reliance on the methods and results of this reference is improper.

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In paragraph #9 of the Declaration, Dr. Fong states that IL-12 was first identified in an MLR in Gubler et al. (PNAS 88: 4143-4147, 1991). However, a review of Gubler et al. does not reveal the use of MLR in evaluating the biological effects of IL-12. Gubler et al. teach that IL-12 is produced by peripheral blood lymphocytes (predominantly B cells) under appropriate conditions and that IL-12 activates NK cells, facilitates the generation of specific allogeneic CTL responses and stimulates secretion of gamma-interferon. Additionally, IL-12 synergizes with IL-2 to cause the proliferation of resting peripheral blood lymphocytes. Therefore, the further work of researchers regarding IL-12 was not based on the results of a single assay, being the MLR, but rather by a body of work which provides for a number of biological activities of IL-12 which are not disclosed for the claimed invention. The claimed invention is not IL-12. Secondly, the methods of Peterson et al. are not disclosed in the instant specification and are after the filing date of the instant application.

In paragraph 10 of the Declaration, Dr. Fong asserts "a PRO polypeptide shown to stimulate T-cell proliferation in the MLR assay of the present invention with an activity of at least 180% of the control is expected to have the type of activity as that exhibited by IL-12". This is an assertion not supported by any facts or evidence of record. First, the instant specification fails to disclose the degree of activity for the claimed invention in the MLR assay. The specification states that any positive increase over control is considered positive; therefore, there is no disclosure that the activity in the assay was at least 180%. Secondly, there is no evidence of record which correlates an activity of at least 180% of control as predictive of an activity of IL-12. It is not clear from what data

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this conclusion is derived. Therefore, the Declaration is not persuasive to overcome the holding of a lack of utility for the claimed invention based on the MLR assay.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39-43, 50-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide having at least 80% amino acid sequence identity to the polypeptide of SEQ ID NO:4 or the mature form thereof, which isolated polypeptide inhibits VEGF stimulated proliferation of adrenal cortical capillary endothelial cells, does not reasonably provide enablement for a polypeptide not identical to at least the mature form of SEQ ID NO:4 which is capable of stimulating proliferation of T-lymphocytes for the reasons of record and for those reasons provided above.

Claim Rejections - 35 USC § 102

Claims 39-43 are rejected under 35 U.S.C. 102(a) as being anticipated by HSIEH et al. (Nature 398: 431-436, 1999) for the reasons of record in the previous Office actions.

Applicant asserts priority of the instant application to September 17, 1998.

However, priority is not granted to this earlier application for the reasons stated above, and the rejection is maintained.

Claims 44-45, 49 are rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over HSIEH et al. (Nature 398: 431-436, 1999) for the reasons of record in the previous Office actions.

Applicant asserts priority of the instant application to September 17, 1998. However, priority is not granted to this earlier application for the reasons stated above, and the rejection is maintained.

Claims 39-43 are rejected under 35 U.S.C. 102(b) as being anticipated by BREWER et al. (WO 98/54963; published 10 December 1998) for the reasons of record in paper #13.

Applicant asserts priority of the instant application to September 17, 1998. However, priority is not granted to this earlier application for the reasons stated above, and the rejection is maintained.

Claims 44-45, 49 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over BREWER et al. (WO 98/54963; published 10 December 1998) for the reasons of record in the previous Office actions.

Applicant asserts priority of the instant application to September 17, 1998. However, priority is not granted to this earlier application for the reasons stated above, and the rejection is maintained.

Conclusion

No claim is allowed.

This is a continuation of applicant's earlier Application No. 09/904,485. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine J. Saoud whose telephone number is 571-272-0891. The examiner can normally be reached on mttr, 8:00-2:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CHRISTINE J. SAoud
PRIMARY EXAMINER

Christine J. Saoud